(12) UK Patent Application (19) GB (11) 2 230 440 (13) A

(43) Date of A publication 24.10.1990

(21) Application No 9002504.0

(22) Date of filing 05.02.1990

(30) Priority data

(31)	(32)	(33)
8902901	09.02.1989	GB
8902898	09.02.1989	
8903147	13.02.1989	
8903663	17.02.1989	

(51) INT CL[5]
A61K 37/02 9/10

(52) UK CL (Edition K)
A5B BJB B180 B31Y B317 B34Y B343 B35Y B351 B822 B829
U1S S1330 S2411

(56) Documents cited
GB 2222770 A WO 90/01329 A JP 61280435 A
JP 01038029 A

(58) Field of search
UK CL (Edition J) A5B BJB BKA
INT CL[4] A61K
Online database: WPI

(71) Applicant
Sandoz Ltd

(Incorporated in Switzerland)

35 Lichtstrasse, CH-4002 Basle, Switzerland

(72) Inventors
Birgit Hauer
Ulrich Posanski

(74) Agent and/or Address for Service
B A Yorke & Co
Coomb House, 7 St John's Road, Isleworth, Middlesex, TW7 6NH, United Kingdom

(54) Cyclosporin compositions

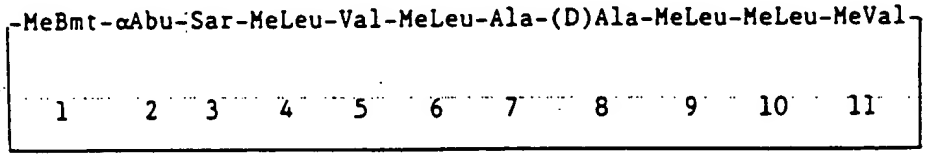
(57) Pharmaceutical compositions comprising (a) a cyclosporin as active ingredient (b) a fatty acid saccharide monoester and (c) a diluent or carrier. Components (c) are typically ethanol, an alkylene glycol (e.g. 1, 2-propylene glycol), an alkylene polyol (e.g. glycerol), a polyalkylene glycol (e.g. PEG, RTM), an alkylene polyol ether or ester paraffin, or an organosilicon oxide polymer. Component (b) may be raffinose monolaurate or sucrose monolaurate. The compositions increase the *in vivo* availability of the cyclosporin.

GB 2 230 440 A

NOVEL CYCLOSPORIN GALENIC FORMS

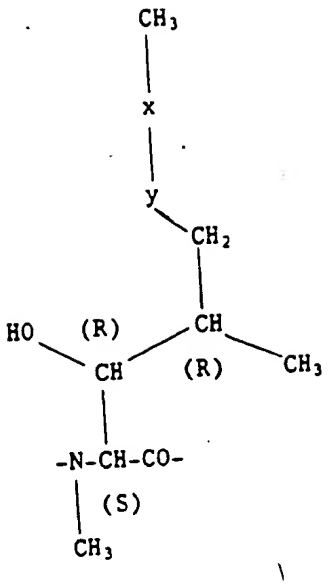
The present invention relates to novel galenic formulations comprising a cyclosporin as active ingredient.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated endecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or Cyclosporine, also known as cyclosporin A and commercially available under the Registered Trade Mark SANDIMMUN^R or SANDIMMUNE^R. Ciclosporin is the cyclosporin of formula A.



(A)

wherein -MeBmt- represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue of formula B



(B)

in which -x-y- is -CH=CH- (trans).

As the parent of the class Ciclosporin has so far received the most attention. The primary area of clinical investigation for Ciclosporin has been as an immunosuppressive agent, in particular in relation to its application to recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and corneal transplants and, in particular, allogenic organ transplants. In this field Ciclosporin has achieved a remarkable success and reputation.

At the same time, applicability of Ciclosporin to various autoimmune diseases and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, has been intensive and reports and results in vitro, in animal models and in clinical trials are wide-spread in the literature. Specific auto-immune diseases for which Ciclosporin therapy has been proposed or applied include, autoimmune hematological disorder (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active

hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Further areas of investigation have been potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis and, yet more recently, use in cancer therapy, e.g. as an agent for reversing or abrogating resistance to other anti-neoplastic or cytostatic therapy.

Since the original discovery of ciclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, Helv. Chim. Acta. 60, 1247-1255 (1977); Traber et al. 2, Helv. Chim. Acta. 65 no. 162, 1655-1667 (1982); Kobel et al., Europ. J. Applied Microbiology and Biotechnology 14, 273-240 (1982); and von Wartburg et al., Progress in Allergy, 38, 28-45 (1986)], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the so called dihydro-cyclosporins [in which the moiety -x-y- of the -MeBmt- residue (Formula B above) is saturated to give -x-y- = $-CH_2-CH_2-$]; derivatised cyclosporins (e.g. in which a further substituent is introduced at the α-carbon atom of the sarcosyl residue at the 3-position of the cyclosporin molecule); cyclosporins in which the -MeBmt- residue is present in isomeric form (e.g. in which the configuration across positions 6' and 7' of the -MeBmt- residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence, employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger - see e.g. Traber 1,

Traber 2 and Kobel loc. cit.; U.S. Patents Nos. 4 108 985, 4 210 581 and 4 220 641; European Patent Publication Nos. 0 034 567, 0 056 782 and 0 296 122; International Patent Publication No. WO 86/02080; Wenger 1, Transp. Proc. 15, Suppl. 1:2230 (1983); Wenger 2, Angew. Chem. Int. Ed., 24, 77 (1985); and Wenger 3, Progress in the Chemistry of Organic Natural Products 50, 123 (1986).

The class comprised by the cyclosporins thus now includes, for example, [Thr]^2-, [Val]^2-, [Nva]^2- and [Nva]^2-[Nva]^5-Ciclosporin (also known as cyclosporins C,D, G and M respectively), [3'-O-acyl-MeBmt]^1-Ciclosporin (also known as cyclosporin A acetate), [Dihydro-MeBmt]^1-[Val]^2-Ciclosporin (also known as dihydro-cyclosporin D), [3'-Desoxy-3'-oxo-MeBmt]^1[Val]^2- and -[Nva]^2-Ciclosporin, [(D)Fluoromethyl-Sar]^3-Ciclosporin, [(D)Ser]^8--Ciclosporin, [MeIle]^{11}-Ciclosporin, [(D)MeVal]^{11}-Ciclosporin (also known as cyclosporin H), [MeAla]^6-Ciclosporin, [(D)Pro]^3-Ciclosporin and so on.

[In accordance with now conventional nomenclature for cyclosporins, these are defined by reference to the structure of Ciclosporin (i.e. Cyclosporin A). This is done by first indicating the amino acid residues present which differ from those present in Ciclosporin (e.g. "[(D)Pro]^3" to indicate that the cyclosporin in question has a -(D)Pro- rather than -Sar- residue at the 3-position) and then applying the term "Ciclosporin" to characterise remaining residues which are identical to those present in Ciclosporin. Individual residues are numbered starting with the residue -MeBmt-, -dihydro-MeBmt- or its equivalent in position 1.]

Very many of these further cyclosporins exhibit comparable pharmaceutical utility to Ciclosporin or more specific utility, for example activity particularly in reversing tumor resistance to cytostatic therapy, and proposals for their application as therapeutic agents abound in the literature.

Despite the very major contribution which Ciclosporin has made, in particular to the areas of organ transplant and the therapy of autoimmune diseases, difficulties encountered in providing more effective and convenient means of administration as well as the reported occurrence of undesirable side reactions, in particular nephrotoxic reaction, have been obvious serious impediments to its wider use or application. The

cyclosporins are characteristically highly hydrophobic. Proposed liquid formulations, e.g. for oral administration of cyclosporins, have hitherto been based primarily on the use of ethanol and oils or similar excipients as carrier media. Thus the commercially available Ciclosporin drink-solution employs ethanol and olive oil as carrier medium in conjunction with labrafil as a surfactant - see e.g. US patent no. 4,388,307. Use of the drink-solution and similar compositions as proposed in the art is however accompanied by a variety of difficulties.

First, the necessity to use oils or oil based carriers may lend the preparations an unpleasant taste or otherwise reduce palatability, in particular for the purposes of long-term therapy. These effects can be masked by presentation in gelatin capsule form. However, in order to maintain the cyclosporin in solution, the ethanol content has to be kept high. Evaporation of the ethanol, e.g. from capsules or from other forms, e.g. when opened, results in the development of a cyclosporin precipitate. Where such compositions are presented in e.g. soft gelatin encapsulated form, this particular difficulty necessitates packaging of the encapsulated product in an air-tight compartment, for example an air-tight blister or aluminium-foil blister-package. This in turn renders the product both bulky and more expensive to produce. The storage characteristics of formulations as aforesaid are far from ideal.

Bioavailability levels achieved using existing oral cyclosporin dosage systems are also low and exhibit wide variation between individuals, individual patient types and even for single individuals at different times during the course of therapy. Thus reports in the literature indicate that currently available therapy employing the commercially available Ciclosporin drink solution provides an average absolute bioavailability of ca. 30% only, with marked variation between individual groups, e.g. between liver (relatively low bioavailability) and bone-marrow (relatively high bioavailability) transplant recipients. Reported variation in bioavailability between subjects has varied from anything between one or a few percent for some patients to as much as 90% or more for others. And as already noted, marked change in bioavailability for individuals with time is frequently observed.

To achieve effective immunosuppressive therapy, cyclosporin blood or blood

serum levels have to be maintained within a specified range. The required range can in turn vary, depending on the particular condition being treated, e.g. whether therapy is to prevent transplant rejection or for the control of an autoimmune disease, and on whether or not alternative immunosuppressive therapy is employed concomitantly with cyclosporin therapy. Because of the wide variations in bioavailability levels achieved with conventional dosage forms, daily dosages needed to achieve required blood serum levels will also vary considerably from individual to individual and even for a single individual. For this reason it is necessary to monitor blood/blood-serum levels of patients receiving cyclosporin therapy at regular and frequent intervals. Monitoring of blood/blood-serum levels, which is generally performed by RIA or equivalent immunoassay technique, e.g. employing monoclonal antibody based technology, has to be carried out on a regular basis. This is inevitably time consuming and inconvenient and adds substantially to the overall cost of therapy.

Beyond all these very evident practical difficulties lies the occurrence of undesirable side reactions already alluded to, observed employing available oral dosage forms.

Various proposals to meet such problems have been suggested in the art, including both solid and liquid oral dosage forms. Thus Japanese patent application no. 71682/1985 to Takada et al. suggests the application of means for increasing the lymphatic delivery of cyclosporins, specifically by administration in conjunction with surfactants. Amongst a general listing of surfactants which may be employed are included, saccharose (sucrose) fatty acid esters, such as saccharose oleate, palmitate or stearate, as well as other fatty acid esters, in particular sorbitan fatty acid esters such as sorbitan oleate, palmitate or stearate. While use of both mono- and poly-esters is indicated, a general preference for mono- or di-esters is proposed. Other surfactants listed include polyoxyethylated hydrogenated vegetable oils such as the products known and commercially available under the trade names Cremophore RH and Nikkol HCO 60, and these are clearly indicated to be preferred, e.g. to the recited saccharose ester surfactants.

Example 3 of the said Japanese application describes obtention of an aqueous preparation comprising a saccharose fatty acid ester, identified as

F160, as surfactant component. The preparation comprises 3.5 mg Ciclosporin and 2mg saccharose ester in 1ml H_2O. To achieve dispersion of the Ciclosporin, sonication for 5 mins. at 100W is required. The obtained preparation, described as "a transparent solution" is employed directly in animal models to investigate relative lymphatic resorption. Given the very lov solubility of Ciclosporin in H_2O and the minor amount of surfactant employed it is evident that the alleged solution is an artefact of the sonification procedure. Not only is the achieved Ciclosporin concentration inappropriately lov, e.g. for an oral dosage form, the preparation is inherently unstable and hence de facto excluded as a practical, or commercial galenic form of any kind. It is essentially an experimental system enabling laboratory investigation and no more. There is no proposal to employ surfactants in any other context than in relation to lymphatic delivery.

Japanese patent application no. 193129/1987 (publication no. 038029/1989), also to Takada et al., discloses powdery preparations comprising a ciclosporin dispersed in a solid, non-surfactant, carrier phase, e.g. comprising sucrose, sorbitol, tartaric acid, urea, cellulose acetate phthallate, methacrylic acid/methyl methacrylate or hydroxypropyl methyl cellulose phthallate, together with minor amounts of a surfactant. Again the surfactant is added with the objective of increasing lymphatic delivery and, in this context, the application is clearly directed towards providing an intended practical means for applying the teachings of the aforementioned Japanese application no. 71682/1985. Reference to saccharose esters as possible surfactant components is in this case omitted. Reference to sorbitan esters amongst a listing of possible surfactant components is retained. However, products of the Nikkol HCO 60 type are again indicated to be preferred as surfactant, and Nikkol HCO 60 is the only surfactant employed in the examples. There is no indication that the alleged increase in lymphatic delivery provides any practical benefit or meets any of the difficulties in cyclosporin therapy hitherto encountered in the art, e.g. as discussed above.

By the present invention there are provided novel cyclosporin galenic formulations comprising fatty acid saccharide monoesters as primary carrier components, which meet or substantially reduce difficulties in cyclosporin, e.g Ciclosporin, therapy hitherto encountered in the art. In

particular it has been found that the compositions of the invention permit the preparation of solid, semi-solid and liquid compositions containing a cyclosporin in sufficiently high concentration to permit, e.g. convenient oral administration, while at the same time achieving improved efficacy, e.g. in terms of bioavailability characteristics.

More particularly it has been found that compositons in accordance with the present invention enable effective cyclosporin dosaging with concomitant enhancement of resorption/bioavailability levels, as well as reduced variability in resorption/bioavailability levels achieved both for individual patients receiving cyclosporin therapy as well as between individuals. By application of the teachings of the present invention cyclosporin dosage forms are obtainable providing reduced variablility in achieved cyclosporin blood/blood serum levels between dosages for individual patients as well as between individuals/ individual patient groups. The invention thus enables reduction of cyclosporin dosage levels required to achieve effective therapy. In addition it permits closer standardisation as well as optimisation of on-going daily dosage requirements for individual subjects receiving cyclosporin therapy as well as for groups of patients undergoing equivalent therapy.

By closer standardisation of individual patient dosaging rate and blood/blood-serum level response, as well as dosaging and response parameters for patient groups, monitoring requirements may be reduced, thus substantially reducing the cost of therapy.

By reduction of required cyclosporin dosaging/standardisation of achieved bio-availability characteristics, the present invention also offers a means permitting reduction in the occurrence of undesirable side-effects, in particular nephrotoxic reaction, in patients undergoing cyclosporin therapy.

In addition, the present invention enables the preparation of compositions which are non-alkanol based, e.g. which may be free or substantially free of ethanol. Such compositions avoid stability and related processing difficulties as hereinbefore discussed, inherent to known alkanolic compositions. The invention thus provides inter al. compositions which are better adapted, e.g. for presentation in capsule, e.g. hard or soft gelatin

capsule form and/or which eliminate or substantially reduce packaging difficulties, for example as hereinbefore discussed, e.g. for soft gelatin encapsulated forms.

More particularly the present invention provides:

A pharmaceutical composition comprising
a) a cyclosporin as active ingredient,
b) a fatty acid saccharide monoester and
c) a diluent or carrier

whereby

i) Component (c) is a solvent with respect to both components (a) and (b), components (a) and (b) each independently having a solubility in component (c) of at least 10% at ambient temperature; or

ii) Component (c) is a solvent with respect to both components (a) and (b), and components (a) and (c) are present in said composition in a ratio of 1:05 to 50 p.p.w. [(a):(c)]; or

iii) Component (c) is a solvent with respect to both components (a) and (b) and said composition is formulated in solid unit dosage form suitable for oral administration; or

iv) Component (c) comprises a poly-(C_{2-4}alkylene)-glycol having an average molecular weight of at most 7,000 or a viscosity at 50°C of at most 15,000 mPa.s. or comprises a C_{3-5}alkylenepolyol ether or ester; or

v) Said composition is, or is substantially, non aqueous; or

vi) Component (c) comprises a solid polymeric carrier, an organo-silicon oxide polymer or paraffinum per- or sub-liquidum and component (a) is present in said composition in solid solution in (b).

The composition thereby defined are novel and particularly advantageous variants of those generically claimed in French patent application no. 88 11953 and corresponding applications in other countries world vide,

including USSN 07/243 577, DOS 38 304945, Japanese application no. 231 396/88 and UK application no. 88 21443.9 (first publicaiton in France, March 17, 1989 under the no. 2 620 336).

Definitions (i) to (vi) above are to be understood as not being mutually exclusive. The compositions of the invention thus embrace compositions as defined complying with any one or more of the defined limitations (i) to (vi). Preferred compositions in accordance with the invention will thus be, for example, such as comply with any two or more of (i) to (v).

The term "pharmaceutical composition" as used herein and in the accompanying claims is to be understood as defining compositions of which the individual components or ingredients are themselves pharmaceutically acceptable, e.g. where oral administration is foreseen, acceptable for oral use or, where topical administration is foreseen, topically acceptable.

The preferred cyclosporin as component (a) is Ciclosporin. A further preferred component (a) is $[Nva]^2$-Ciclosporin, also known as cyclosporin G.

Preferred components (b) for use in the compositions of the invention are water soluble fatty acid saccharide monoesters, e.g. fatty acid monoesters of saccharides having a solubility in water of at least 3.3% at ambient temperature, i.e. which are dissolvable in water at ambient temperature in an amount of at least 1g monoester per 30 ml water.

The fatty acid moiety of components (b) may comprise saturated or unsaturated fatty acids or mixtures thereof. Particularly suitable components (c) are C_{6-18}-fatty acid saccharide monoesters, in particular water soluble C_{6-18}-fatty acid saccharide monoesters. Especially suitable components (c) are caproic (C_6), caprylic (C_8), capric (C_{10}), lauric (C_{12}), myristic (C_{14}), palmitic (C_{16}), oleic (C_{18}), ricinoleic (C_{18}) and 12-hydroxystearic (C_{18}) acid saccharide monoesters, especially lauric acid saccharide monoesters.

The saccharide moiety of component (b) may comprise any appropriate sugar residue, e.g. mono-, di- or tri-saccharide residue. Suitably, the saccharide moiety will comprise a di- or tri-saccharide residue. Preferred components (b) comprise C_{6-14}-fatty acid di-saccharide monoesters and

C_{8-18}-fatty acid tri-saccharide monoesters.

Especially suitable saccharide moieties are saccharose and raffinose residues. Particularly suitable components (b) are thus: saccharose monocaproate, saccharose monolaurate, saccharose monomyristate, saccharose monooleate, saccharose monoricinoleate, raffinose monocaproate, raffinose monolaurate, raffinose monomyristate, raffinose monopalmitate and raffinose monooleate. Most preferred components (b) are raffinose monolaurate and. especially, saccharose monolaurate

Components (b) will suitably have a hydrophilic-lipophilic balance (HLB) of at least 10.

Components (b) suitably have an ester residue purity of at least 80%, more preferably at least 90%, most preferably at least 95%. Components (b) suitably have a melting point of from about 15° to about 60°C, more preferably from about 25° to about 50°C.

By definitions (ii) and (iii) as hereinabove applied to the compositions of the invention, components (c) defined are materials in which both components (a) and (b) exhibit substantial solubility at ambient temperature, e.g. at temperatures of ca. 20°C. Preferred components (c) are materials in which (a) and (b) independently have a solubility of at least 10% [as required by definition (i)], preferably at least 25%, most preferably at least 50% (e.g. in which components (a) or (b) independently have a solubility of the order of at least 100mg, preferably 250mg, most preferably at least 500 mg/ml) at ambient temperature. Especially preferred are materials in which component (a) has a solubility of at least 10%, preferably at least 25%, most preferably at least 50% and/or in which component (b) has a solubility of at least 100%, more preferably at least 200%, most preferably at least 300% (e.g. in which component (b) has a solubility of the order of at least 1,000, more preferably 2,000, most preferably at least 3,000 mg/ml).

Components (c) suitable for use in the compositions of the invention include:

c^1) ethanol;

c^2) C_{2-4}alkylene glycols;

c^3) C_{3-5}alkylene-polyols;

c^4) poly-(C_{2-4}alkylene)glycols; and

c^5) C_{3-5}alkylene-polyol ethers or esters,

as well as any mixture thereof.

In accordance with the general objectives of the invention, the use of ethanol, whether alone or in admixture with any other component (c), will however generally be less preferred.

When component (c) comprises a C_{2-4}alkylene glycol (c^2), this is preferably a propylene glycol, most preferably 1,2-propylene glycol. When component (c) comprises a C_{3-5}alkylene polyol (c^3), this is preferably a C_{3-5}alkylene triol, most preferably glycerol.

When component (c) comprises a poly-(C_{2-4}alkylene)glycol (c^4), this is suitably a polyethylene glycol. For use in the compositions of the invention, such components preferably have an average molecular weight of not more than about 7,000 [cf. definition (iv)], e.g. up to 6,600, more preferably of not more than about 2,000, e.g. up to 1,600, most preferably of not more than about 500. Preferably such components have a viscosity of at most about 15,000 mPa.s., more preferably at most about 1,000 mPa.s., most preferably at most about 200 mPa.s., at 50°C or, more suitably, at ambient temperatures [cf. definition (iv)]. Suitable polyethylene glycols for use as components (c) are, e.g. as described in Fiedler, Lexikon der Hilfstoffe, 2nd. revised and expanded edition, [1981] Vol. 2, at pages 726 to 731, in particular the products PEG (polyethylene glycol) 200, 300, 400 and 600, as well as PEG 1000, 2000, 4000 or 6000, but especially 200, 300 and 400, e.g. conforming to the following approximate physical characteristics:

	PEG 200	PEG 300	PEG 400	PEG 600
mol. wt.	ca. 190-210	ca. 285-215	ca. 380-420	ca. 570-630
viscosity mPa.s.	ca. 46-53	ca. 66-74	ca. 85-95	ca. 130-150
freezing point	ca. -50°C	ca. -16 to -12°C	ca. -3 to 8°C	ca. 15 to 25°C
n_D^{25}	ca. 1.459	ca. 1.463	ca. 1.465	ca. 1.467

When component (c) comprises a C_{3-5}alkylene polyol ether or ester (c^5), this is suitably a C_{3-5}alkylene triol, in particular glycerol, ether or ester. Suitable components (c^5) include mixed ethers or esters, i.e. components including other ether or ester ingredients, for example transesterification products of C_{3-5}alkylene triol esters with other mono-, di- or poly-ols.

Particularly suitable components (c^5) are mixed C_{3-5}alkylene triol/poly-(C_{2-4}alkylene) glycol fatty acid esters, especially mixed glycerol/polyethylene- or polypropylene-glycol fatty acid esters.

Especially suitable components (c^5) for use in accordance with the present invention include products obtainable by transesterification of glycerides, e.g. triglycerides, with poly-(C_{2-4}alkylene) glycols, e.g. poly-ethylene glycols and, optionally, glycerol. Such transesterification products are generally obtained by alcoholysis of glycerides, e.g. triglycerides, in the presence of a poly-(C_{2-4}alkylene) glycol, e.g. polyethylene glycol and, optionally, glycerol (i.e. to effect transesterification from the glyceride to the poly-alkylene glycol/glycerol component, i.e. via poly-alkylene glycolysis/glycerolysis). In general such reaction is effected by reaction of the indicated components (glyceride, polyalkylene glycol and, optionally, glycerol) at elevated temperature under an inert atmosphere with continuous agitation.

Preferred glycerides are fatty acid triglycerides, e.g. (C_{10-22}fatty acid) triglycerides, including natural and hydrogenated oils, in particular vegetable oils. Suitable vegetable oils include, for example, olive, almond, peanut, coconut, palm, soybean and wheat germ oils and, in particular, natural or hydrogenated oils rich in (C_{12-16}fatty acid) ester residues.

Preferred polyalkylene glycol materials are polyethylene glycols, in particular polyethylene glycols having a molecular weight of from ca. 500 to ca. 4,000, e.g. from ca. 1,000 to ca. 2,000.

Suitable components (c^5) thus comprise mixtures of C_{3-5}alkylene triol esters, e.g. mono-, di- and tri-esters in variable relative amount, and poly(C_{2-4}alkylene) glycol mono- and di-esters, together with minor amounts of free C_{3-5}alkylene triol and free poly-(C_{2-5}alkylene) glycol. As hereinabove set forth, the preferred alkylene triol moiety is glyceryl; preferred polyalkylene glycol moieties will be polyethylene glycyl, in particular having a molecular weight of from ca. 500 to ca. 4,000; and preferred fatty acid moieties will be C_{10-22}fatty acid ester residues, in particular saturated C_{10-22}fatty acid ester residues.

Particularly suitable components (c^5) may thus alternatively be defined as: transesterification products of a natural or hydrogenated vegetable oil and a polyethylene glycol and, optionally, glycerol; or compositions comprising or consisting of glyceryl mono-, di- and tri- C_{10-22}fatty acid esters and polyethylene glycyl mono- and di- C_{10-22}fatty acid esters (optionally together with, e.g. minor amounts of free glycerol and free polyethylene glycol).

Preferred vegetable oils, polyethylene glycols or polyethylene glycol moieties and fatty acid moieties in relation to the above definitions are as hereinbefore set forth. Particularly suitable componets (c^5) as described above for use in the present invention are those known and commercially available under the trade name Gelucir, in particular the products

i) Gelucir 33/01, which has an m.p. = ca. 33-38°C and a saponification no. = ca. 240/260;

ii) Gelucir 35/10, m.p. = ca. 29-34°C, saponification no. = ca. 120-140;

iii) Gelucir 37/02, m.p. = ca. 34-40°C, saponification no. = ca. 200-220;

iv) Gelucir 42/12, m.p. = ca. 41-46°C, saponification no. = ca. 95-115;

v) Gelucir 44/14, m.p. = ca. 42-46°C, saponification no. = ca. 75-95;

vi) Gelucir 46/07, m.p. = ca. 47-52°C, saponification no. = ca. 125-145;

vii) Gelucir 48/09, m.p. = ca. 47-52°C, saponification no. = ca. 105-125;

viii) Gelucir 50/02, m.p. = ca. 48-52°C, saponification no. = ca. 180-200;

ix) Gelucir 50/13, m.p. = ca. 46-41°C, saponification no. = ca. 65-85;

x) Gelucir 53/10, m.p. = ca. 48-53°C, saponification no. = ca. 95-115;

xi) Gelucir 62/05, m.p. = ca. 60-65°C, saponification no. = ca. 70-90.

Products (i) to (x) above all have an acid value = <2. Product (xi) has an acid value = <5. Products (ii), (iii) and (vi) to (x) above all have an iodine no. = <3. Product (i) has an iodine no. = ≤8. Products (iv) and (v) have an iodine no. = <5. Product (xi) has an iodine no. = <10. Components (c^5) having an iodine no. = <1 will generally be preferred. As will be appreciated, mixtures of components (c^5) as defined may also be employed in the compositions of the invention.

When a component (c) as hereinabove particularly described [i.e. component complying with any of the definitions (i) to (iv) hereinabove or any component as defined under (c^1) to (c^5)] is employed, the compositions of

the invention will generaly comprise component (a) in a carrier medium comprising components (b) and (c). Commonly components (a) and (b) will each be present in the compositions of the invention in dispersion or solution, e.g. molecular or miscellar dispersion or solution, (including. where appropriate, solid solution). Thus component (a) will generally be present in dispersion or solution in both components (b) and (c) and components (b) will in turn be present in solution in (c). Component (b) will generally act in the compositions of the invention as a carrier or solubilizor (either pre- and/or post-administration) for component (a), and component (c) will act as a carrier or fluidizer. (The present invention is, of course, not to be understood as being in anyway restricted to any particular functional relationship between the components (a), (b) and (c), unless otherwise specified.)

It is further preferred that, when a component (c) as aforesaid is employed, the compositions of the invention should be formulated in solid unit dosage form suitable for oral administration, for example presented in hard or soft gelatin encapsulated form suitable for oral administration [cf. definition (iii)]. Such unit dosage forms will, as hereinafter described in greater detail, suitably comprise, e.g. from 2 to 200mg of component (a) per unit dose.

When a component (c) as aforesaid is employed, components (a) and (c) will preferably be present in the compositions of the invention in a ratio of from 1:0.5 to 50 p.p.w. [(a):(c)] [cf. definition (ii)]. Components (a) and (b) will suitably be present in a ratio of from 1:3 to 200 p.p.w. [(a):(b)].

When a component (c) as aforesaid is employed it is yet further preferred that the compositions of the invention should be non-aqueous or substantially non-aqueous [cf. definition (v)], e.g. have a water content of less than 20%, more preferably less than 10%, yet more preferably less than 5%, 2%, or 1%, based on the total weight of the composition.

In accordance with the foregoing, the present invention also provides, in a series of particular embodiments:

- A pharmaceutical composition comprising a component (a) and a component

(b) as hereinbefore defined and a diluent selected from any one of components (c^1) to (c^4) as hereinbefore defined, or any mixture thereof, and complying with anyone of definitions (ii) to (v) hereinabove;

- A pharmaceutical composition comprising a component (a), (b) and (c^2) as hereinbefore defined and complying with definitions (ii), (iii) or (v) hereinabove; and

- A pharmaceutical composition comprising a component (a), (b) and (c^5) as hereinbefore defined.

When a component (c) as hereinbefore particularly described [i.e. component complying with anyone of the definitions (i) to (iv) or any of components (c^1) to (c^5)] is employed in the said compositions of the invention, components (a) and (c) are suitably present in said compositions in a ratio of about 1:0.5 to 50 p.p.w. More suitably components (a) and (c) are present in a ratio of about 1:1 to 10, more preferably 1:1 to 5, most preferably about 1:1.5 to 2.5, e.g. about 1:1.6 or 1:2 p.p.w. [(a):(c)]. Components (a) and (b) are suitably present in the said compositions in a ratio of about 1:3 to 200, preferably about 1:3 to 100, more preferably about 1:3 to 50 p.p.w. More suitably components (a) and (b) are present in a ratio of about 1:5 to 20, preferably about 1:5 to 10, most preferably about 1:6.0 to 6.5, e.g. about 1:6.25 p.p.w. [(a):(b)].

When the compositions of the invention comprise saccharose monolaurate as component (b) and 1,2-propylene glycol as component (c), components (a) and (b) are preferably present in a ratio of from about 1:6 to 7 p.p.w. [(a):(b)] and components (a) and (c) are preferably present in a ratio of from about 1:1.5 to 2.5, e.g. about 1:2 p.p.w. [(a):(c)].

Compositions in accordance with the present invention comprising a component (c) as aforesaid may be made up in any appropriate dosage form, e.g. for oral, parenteral or topical application, for example for dermal or ophthalmic application, e.g. for application to the surface of the eye, e.g. for the treatment of autoimmune conditions of the eye such as hereinbefore set forth, or for intralesional injection, e.g. in the treatment of psoriasis.

Suitably such compositions will be made up in unit dosage form, whether for oral administration or otherwise.

The amount of component (a) present in such unit dosage forms will of course vary depending on e.g. the condition to be treated, the intended mode of administration and the effect desired. In general however, such unit dosage forms will suitably comprise from about 2 to about 200 mg component (a), e.g. Ciclosporin, per unit dosage.

Suitable dosage forms for oral administration include e.g. liquids, granulates and the like. Preferred however are solid unit dosage forms, for example tabletted or encapsulated forms, in particular hard or soft gelatin encapsulated forms. Such oral unit dosage forms will suitably comprise from about 5 to about 200 mg, more suitably from about 10 or 20 to about 100 mg, e.g. 15, 20, 25, 50, 75 or 100 mg, component (a), e.g. Ciclosporin, per unit dosage.

Compositions in accordance with the present invention comprising a component (c) as aforesaid have the further advantage that they are capable of providing the basis for compositions exhibiting modified release characteristics, for example delayed release of component (a) or release of component (a) over prolonged periods of time, e.g. following oral administration. Such compositions additionally comprise (d), a component capable of modifying the release characteristics of the composition with respect to component (a). Such components (d) include, for example, polymeric excipients, in particular thickening agents, e.g. polymeric or colloidal thickening agents, as well as agents which are swellable in water, e.g. water-swellable polymers or colloids.

Suitable components (d) are known from the art and include:

d¹) Polyacrylate and polyacrylate co-polymer resins, for example poly-acrylic acid and poly-acrylic acid-methacrylic acid resins, such as known and commercially available under the trade name Carbopol (c.f. Fiedler, loc. cit., 1, p.p. 206-207), in particular the products Carbopol 934, 940 and 941, and Eudragit (c.f. Fiedler, loc. cit., 1, p.p. 372-373), in particular the products Eudragit E, L, S, RL and RS and, most especially, the products Eudragit E, L and S;

d^2) Celluloses and cellulose derivatives including: alkyl celluloses, e.g. methyl-, ethyl- and propyl-celluloses; hydroxyalkyl-celluloses, e.g. hydroxypropyl-celluloses and hydroxypropylalkyl-celluloses such as hydroxypropyl-methyl-celluloses; acylated celluloses, e.g. cellulose-acetates, cellulose-acetatephthallates, cellulose-acetatesuccinates and hydroxypropylmethyl-cellulose phthallates; and salts thereof such as sodium-carboxymethyl-celluloses. Examples of such products suitable for use in accordance with the present invention are those known and commercially available, e.g. under the trade names Klucel and Methocel (c.f. Fiedler, loc. cit., 1. p.p. 521 and 2, p.p. 601), in particular the products Klucel LF, MF, GF and HF and Methocel K 100, K 15M, K 100M, E 5M, E 15, E 15M and E 100M.

d^3) Polyvinylpyrrolidones, including for example poly-N-vinylpyrrolidones and vinylpyrrrolidone co-polymers such as vinylpyrrolidone-vinylacetate co-polymers. Examples of such compounds suitable for use in accordance with the present invention are those known and commercially available, e.g. under the trade name Kollidon (c.f. Fiedler, loc. cit., 1, p.p. 526 and 527), in particular the products Kollidon 30 and 90.

d^4) Polyvinyl resins, e.g. including polyvinyl acetates and polyvinyl alcohols, as well as other polymeric materials including gum traganth, gum arabicum, alginates, e.g. alginic acid, and salts thereof, e.g. sodium alginates.

d^5) Silicon dioxides, including hydrophilic silicon dioxide products, e.g. alkylated (for example methylated) silica gels, in particular colloidal silicon dioxide products as known and commercially available under the trade name Aerosil [c.f. Handbook of Pharmaceutical Excipients, published by the Pharmaceutical Society of Great Britain, p.p. 253 to 256] in particular the products Aerosil 130, 200, 300, 380, 0, OX 50, TT 600, MOX 80, MOX 170, LK 84 and the methylated Aerosil R 972.

When a component (d) is present, it is suitably present in an amount of from about 0.5 to 50%, more preferably from about 1 to 20%, most preferably from about 2 to 10% by weight, based on the total weight of components (a)+(b)+(c)+(d).

When component (c) in the compositions of the invention comprises: (c^6) a solid polymeric carrier as required by definition (vi) hereinbefore, this is preferably a water insoluble, or substantially water insoluble, polymeric carrier.

Especially preferred as components (c^6) are polyvinylpyrrolidones [c.f. Fiedler, loc. cit., 2, p.p. 748-750], including, especially, cross-linked polyvinylpyrrolidones. Examples of such materials suitable for use in the present invention are those known and commercially available under the trade name Kollidon [c.f. Fiedler, loc. cit., 1, p.p. 527], Kollisept [c.f. Fiedler, loc. cit., 2, p.p. 719-720], Povidone and Crospovidone [c.f. Fiedler, loc. cit., 2, p.p. 751].

Especially suitable components (c^6) are polyvinylpyrrolidones having a molecular weight of at least ca. 10,000 more suitably at least ca. 20,000 or 25,000, e.g. having a molecular weight of ca. 40,000 or more. Cross-linked polyvinylpyrrolidones are of particular interest. Examples of specific products suitable for use in the present invention as (c^6) are: Plasdone XL, Plasdone XL 10 and Crospovidone.

When the compositions of the invention comprise a component (c^6) they preferably also comprise (d), a water swellable or water soluble component, for example a cellulose or cellulose derivative as defined under (d^2) hereinabove.

Further examples of such materials of particular interest in relation to compositions of the invention comprising a component (c^6) are those known and commercially available under the trade names Avicel [c.f. Fiedler, loc. cit., 1, p.p. 160-161], Elcema [c.f. Fiedler, loc. cit., 1, p.p. 326] and Pharmacoat [c.f. Fiedler, loc. cit., 2, p.p. 707], for example the products Avicel PH 101 and PH 102, Elcema and Pharmacoat 603.

In the case of compositions of the invention comprising a component (c^6), component (a) is present in component (b) in solid solution, including solid miscellar solution, e.g. entirely, or substantially entirely, in molecular or miscellar dispersion, [In practice components (b) will frequently exhibit at least a degree of fluidity, e.g. at ambient or

slightly elevated temperature, and hence not be in the strictest sense "solid". The term "solid solution" as used in the present specification and claims is to be interpreted accordingly, e.g. as including viscous or highly viscous systems.] The solid solution comprised by (a) and (b) is suitably dispersed, for example in particulate, e.g. fine particulate form within, e.g. throughout, component (c^6). Components (c^6) will thus generally serve in compositions of the invention as a disintegratable matrix for [(a)+(b)]. Components (d) will generally serve as agents assisting disintegration, e.g. on contact with the contents of the gastro-intestinal tract.

Compositions of the invention comprising a component (c^6) will also suitably comprise (e), a binder and/or lubricant. Materials suitable for use as binding agent/lubricants are in particular fatty acid and alkyl sulfonate salts, e.g. metal salts, e.g. having 10 or more carbon atoms in the fatty acid/alkyl moiety, for example C_{10-22} fatty acid and C_{10-22}alkyl sulfonate alkali metal or alkaline earth metal salts, e.g. sodium calcium or magnesium salts. Examples of such materials suitable for use in the present invention are: sodium lauryl sulfate and magnesium stearate [c.f. Fiedler, loc. cit., 2, p.p. 584].

When compositions of the invention comprise a component (c^6), components (a) and (b) are suitably present in a ratio of about 1:2 to 20, preferably about 1:2.5 to 10, most preferably about 1:3 to 8 [(a):(b)].

Components (c^6) are suitably present in compositions of the invention in an amount of at least 10%, more preferably at least 15%, yet more preferably at least 20% by weight based on the total weight of the composition. Appropriately components (c^6) are present in compositions of the invention in an amount of from 10 to 60%, more preferably of from 15 to 50% by weight, e.g. from ca. 20 to 40%, e.g. ca. 25, 30 or 35% by weight, based on the total weight of the composition.

When a component (d) is present, components (d) and (c^6) are suitably present in a ratio of ca. 1:0.5 to 4, more preferably ca. 1:1 to 3, most preferably ca. 1:1.5 to 2.5, e.g. ca. 1:2 or ca. 1:2.5 p.p.w. [(d):(c^6)].

When a component (e) is present, components (e) and (c^6) are suitably

present in a ratio of ca. 1:5 to 25, more preferably ca. 1:5 to 20, most preferably ca. 1:7 to 15 p.p.w. [(e):(c^6)].

When the compositions of the invention comprise all three components (c^6), (d) and (e) these are suitably together present in an amount of from ca. 25 to 75%, more preferably ca. 30 to 65%, most preferably ca. 40 to 65% based on the total weight of the composition. The ratio of components [(a)+(b)]:[(c)+(d)+(e)] is suitably of the order of 1:0.25 to 7.5, more preferably 1:0.5 to 5, most preferably 1:0.5 to 2, e.g. ca. 1:0.8, 1:1.2 or 1:1.3 p.p.w.

Compositions in accordance with the invention comprising a component (c^6) may be made up in any appropriate dosage form, e.g. for oral, parenteral or topical application. Suitably such compositions in accordance with the invention will be made up in unit dosage form, whether for oral administration or othervise.

The amount of component (a) present in such unit dosage forms will of course vary depending on e.g. the condition to be treated, the intended mode of administration and the effect desired. In general however they will suitably comprise from about 2 to about 200 mg component (a), e.g. Ciclosporin, per unit dosage.

Suitable dosage forms for oral administration include granulates and the like. Preferred however are solid unit dosage forms, for example tabletted or encapsulated forms. Such oral unit dosage forms will suitably comprise from about 5 to about 200 mg, more suitably from about 10 or 20 to about 100 mg, e.g. 15, 20, 25, 50, 75 or 100 mg, component (a), e.g. Ciclosporin, per unit dosage.

When component (c) in the compositions of the invention comprises: (c^7) an organosilicon oxide polymer or paraffinum per- or subliquidum as required by definition (vi) hereinbefore, component (c^7) is preferably readily flovable at temperatures of up to 150°C, preferably up to 100°C, more preferably up to 50°C. Suitably components (c^7) have a maximum viscosity of 15,000 mPa.s., more preferably 1,000 mPa.s. at the indicated temperatures.

Paraffin hydrocarbons suitable for use as component (c^7) are liquid and semi-solid paraffins and mixtures thereof, i.e. paraffinum subliquidum and paraffinum perliquidum [see Fiedler loc.cit., 2, p.p. 690-691]. To permit ready formulation, component (c^7) suitably consists or consists essentially of fluid, or semi-solid paraffins, i.e. paraffinum perliquidum or paraffinum subliquidum, or mixtures thereof. Where however it is desired to produce compositions having e.g. slover active ingredient release characteristics, this may be achieved by the further addition of a solid paraffin, i.e. paraffinum durum.

When compositions in accordance with the invention comprise liquid or semi-solid paraffins only as component (c^7) these are preferably present in a ratio of from ca. 1:0.5 to 1.0 [liquid: semi-solid]. In this case components (a) and (c^7) are suitably present in a ratio of from ca. 1:6 to 200, more preferably ca. 1:6 to 100, most preferably 1:6 to 20, e.g. ca. 1:8 p.p.w. [(a):(c)].

When compositions in accordance with the invention additionally comprise a solid paraffin as component (c^7), the ratio of liquid/semi-solid paraffin:solid paraffin components is suitably ca. 1:0.06 to 0.1 p.p.w. In this case components (a) and (c^7) are suitably present in a ratio of from 1:6 to 200, more preferably 1:6 to 100, most preferably 1:8 to 20, e.g. ca. 1:10 p.p.w. [(a):(c^7)].

Organosilicon oxide polymers suitable for use as component (c^7) include, in particular, fluid, i.e. liquid and semi-solid polymeric materials having a structural unit of formula $-(R)_2Si-O-$ in which R is a monovalent organic radical, for example C_{1-4} alkyl, especially methyl, or phenyl. Especially preferred are organosiloxane polymers having a viscosity of from ca. 0.65 to 10^5 cP, especially of from ca. 10 or 50 to 500 or 1,000 cP.

To permit ready formulation, component (c^7) suitably comprises liquid organosiloxane polymers, e.g. poly-methylsiloxane polymers, e.g. any of the various known silicon oils, such as silicon oil 550, DC 200, SF-1066 and SF-1091 [c.f. Fiedler, loc. cit., 2, p.p. 826]. When compositions in accordance with the invention comprise liquid organosiloxane polymers only, components (a) and (c^7) are suitably present in a ratio of from ca. 1:6 to 200, more preferably ca. 1:6 to 100, most preferably 1:6 to 20, e.g. ca.

1:8 p.p.w. [(a):(c^7)].

Compositions having e.g. slover active ingredient release characteristics may be achieved use of semi-solid organosiloxane polymers, e.g. any of the various known silicon pastes, e.g. silicon paste A [c.f. Fiedler, loc. cit., 2, p.p. 826] as component (c^7) or by addition of these, e.g. to other organosilicon oxide polymers as described above. In the latter case, the ratio of liquid:semi-solid organosilicon polymers present in the composition of the invention is suitably of the order of from ca. 1:0.5 to 1. In this case the ratio of components (a):(c^7) is suitably of the order of from ca. 1:6 to 100, preferably ca. 1:6 to 20 p.p.w. [(a):(c^7)].

As will be appreciated, mixtures of components (c^7) as defined may also be employed in the compositions of the invention.

When compositions of the invention comprise a component (c^7), components (a) and (b) are suitably present in a ratio of about 1:6 to 20, preferably about 1:6 to 10, most preferably about 1:6.0 to 6.5, e.g. about 1:6.25 p.p.w. [(a):(b)].

In the case of compositions of the invention comprising a component (c^7), component (a) is present in component (b) entirely, or substantially entirely in molecular or miscellar dispersion, e.g. in the form of a solid solution or solid miscellar solution [whereby the term "solid solution" is employed here in the same broad sense as in relation to compositions a component (c^6)]. The solid solution comprised by (a) and (b) is suitably dispersed in particulate, e.g. fine particulate, form with component (c^7), e.g. throughout component (c^7).

Compositions in accordance with the invention comprising a component (c^7) may be made up in any appropriate dosage form, e.g. for oral, parenteral or topical application, for example for dermal or ophthalmic application, e.g. for application to the surface of the eye, e.g. for the treatment of autoimmune conditions of the eye such as hereinbefore set forth, or for intra-lesional injection, e.g. in the treatment of psoriasis. Suitably they will be made up in unit dosage form, whether for oral administration or otherwise.

The amount of component (a) present in such unit dosage forms will of course vary depending on e.g. the condition to be treated, the intended mode of administration and the effect desired. In general however, they will suitably comprise from about 2 to about 200 mg component (a), e.g. Ciclosporin, per unit dosage.

Suitable dosage forms for oral administration include liquids, granulates and the like. Preferred however are solid unit dosage forms, for example tabletted or encapsulated forms, in particular hard or soft gelatin encapsulated forms. Such oral unit dosage forms will suitably comprise from about 5 to about 200 mg, more suitably from about 10 or 20 to about 100 mg, e.g. 15, 20, 25, 50, 75 or 100 mg, component (a), e.g. Ciclosporin, per unit dosage.

Compositions in accordance with the invention comprising a component (c^7) have the further advantage that they are capable of providing the basis for compositions exhibiting modified release characteristics, for example delayed release of component (a), or release of component (a) over prolonged periods of time, e.g. following oral administration. Such compositions may be obtained as hereinbefore described by the inclusion of solid or semi-solid components (c^7) in appropriate amounts. Alternatively they may be obtained by inclusion of an additional component (d): a component capable of modifying the release characteristics of the composition with respect to component (a). Such components (d) include, for example, polymeric excipients, in particular thickening agents, e.g. polymeric or colloidal thickening agents, as well as agents which are swellable in water, e.g. water-swellable polymers or colloids, for example any of the materials defined under (d^1) to (d^5) hereinabove.

When a component (d) is present, this is suitably present in an amount of from about 0.5 to 30%, more preferably from about 1 to 20%, most preferably from about 1 to 10% based on the total weight of components (a)+(b)+(c^7)+(d).

Components (d^5) are in particular indicated for use in compositions in accordance with the invention comprising an organosilicon oxide polymer as component (c^7).

Compositions in accordance with the invention comprising a component (c^6) or (c^7) will be, or will preferably be, non-aqueous or substantially non-aqueous, e.g. as hereinabove described in relation to compositions comprising other components (c).

Compositions in accordance with the present invention may, irrespective of the selected component (c) [e.g. whether component (c) comprises any one of components (c^1) to (c^7) hereinbefore set forth or any mixture thereof] include any additional additives, e.g. as known and conventionally employed in the art, for example antioxidants [e.g. ascorbyl-palmitate, tocopherols, butyl-hydroxy-anisole (BHA) or butyl-hydroxy-toluene (BHT)], flavouring agents and so forth.

In particular the compositions of the invention will also suitably comprise one or more stabilizors or buffering agents, in particular to prevent hydrolysis of component (b) or degradation of component (a) during processing or on storage. Such stabilizors may include acid stabilizors such as citric acid, acetic acid, tartaric acid or fumaric acid as well as basic stabilizors such as potassium hydrogen phosphate, glycine, lysine, arginine or tris(hydroxymethyl)aminomethane.

Such stabilizors or buffer agents will appropriately be added in an amount sufficient to achieve or maintain a pH within the range of from about 3 to 8, more preferably about 5 to 7, e.g. between 6 and 7. Such stabilizors will generally be present in an amount of up to 5% by weight based on the total weight of the composition, or up to 10% by weight, for example where citric or acetic acids are employed. Compositions in accordance with the invention, in particular compositions wherein component (a) is Ciclosporin, having a pH within the above indicated ranges are preferred.

Compositions in accordance with the invention will also suitably comprise a polyoxyalkylene-free tenside, such as for example dioctylsuccinate, dioctyl-sulfo-succinate, di[2-ethylhexy]-succinate, sodium lauryl sulfate or phospholipids, e.g. lecithins. When a tenside as aforesaid is present, this is suitably present in an amount of from 5 to 50, more preferably 10 to 50, for example 10 to 25% based on the weight of component (b).

In the case of compositions of the invention comprising component (a) in

solid solution in component (b), e.g. when component (c) is a component (c^6) or (c^7) as hereinbefore set forth, any stabilizors, buffers and/or tensides as aforesaid are suitably incorporated into the solid solution phase. Such materials may also be included in component (c) etc..

Compositions in accordance with the invention, again irrespective of the selected component (c), will preferably be free or substantially free of ethanol, e.g. contain less than 5.0%, more preferably less than 2.5%, e.g. from 0 to 1.0% of ethanol based on the total weight of the composition.

In addition to the foregoing, the present invention also provides a process for the preparation of a pharmaceutical composition as hereinbefore defined, which process comprises intimately admixing or compounding components (a), (b) and (c) as hereinbefore defined, optionally together with a component (d) and/or other component, e.g. stabilizor, buffer or tenside as hereinbefore described, and, when required, putting the obtained composition up in unit dosage form, for example unit dosage form for oral administration, e.g. by tabletting, filling into gelatin capsules or other suitable means.

When component (c) is a solvent for components (a) and (b), or comprises a component (c^1), (c^2), (c^3), (c^4) or (c^5) as hereinbefore defined, components (a), (b) and (c) are suitably brought together in the above process by dissolution of components (a) and (b) together in component (c), e.g. with warming at temperatures of from up to 50° or 150°C, preferably not above 70 or 75°C. The mixture thus obtained may then be further compounded with components (d) etc..., e.g. by intimate admixture in accordance with techniques known in the art. Filling, e.g. into hard or soft gelatin capsules, is suitably performed at elevated temperature, e.g. up to 50°C, to attain composition fluidity, e.g. in the warm.

In the case of compositions in accordance with the invention comprising component (a) in solid solution in component (b), e.g. compositions comprising a component (c^6) or (c^7) as hereinbefore set forth, said process will suitably first comprise preparation of a solid solution of (a) in (b) followed by intimate admixture or compounding of the obtained solid solution with the remaining components (c) and, optionally, (d) etc..

Solid solutions comprising components (a) in (b) may be prepared in accordance with techniques known in the art, e.g. by solidification of a melt comprising (a) in solution in (b), or removal of the solvent from a solution of components (a) and (b). For the purposes of the present invention the latter alternative will generally be preferred.

Suitable solvents for components (a) and (b) include lower alkanols, e.g. ethanol. Stabilizors, buffers and/or tensides are suitably incorporated at the solution stage.

The solid solution thus obtained is then suitably compounded, e.g. in fine particulate form, with component (c) and, optionally, components (d) and (e) etc..., e.g. by distribution in component (c).

Although ethanol may be employed for the purpose of preparing the compositions of the invention, e.g. in the preparation of solid solutions as described above, this will preferably be removed, e.g. by evaporation, prior to completion of the final dosage form to give an ethanol free or substantially ethanol free product as hereinbefore set forth.

The following examples are illustrative of the present invention.

The product saccharose monolaurate L-1969 employed in the examples is commercially available from Mitsubishi-Kasei Food Corp., Tokyo 104, Japan: HLB-value = at least 12.3: lauryl ester residue purity = at least 95%: M.P. = ca. 35°C: decomposition at ca. 235°C: surface tension of 0.1% by weight aqueous solution = ca. 72.0 dyn/cm at 25°C.

EXAMPLES

	INGREDIENT	RELATIVE AMOUNT (mg)
1. a)	Cyclosporin (e.g. Ciclosporin)	50.0
b)	Saccharose monolaurate L-1695	312.5
c)	1,2-propylene glycol	100.0
	TOTAL	462.5

2.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	312.5
	c)	Glycerol	100.0
		TOTAL	462.5
3.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	312.5
	c)	PEG 200	100.0
		TOTAL	462.5
4.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	312.5
	c)	PEG 400	100.0
		TOTAL	462.5
5.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	350.0
	c)	1,2-propylene glycol	100.0
	d)	Eudragit E	50.0
		TOTAL	550.0
6.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	350.0
	c)	1,2-propylene glycol	100.0
	d)	Methocel K100	110.0
		TOTAL	610.0
7.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	350.0
	c)	1,2-propylene glycol	100.0
	d)	Aerosil 200	15.0
		TOTAL	515.0
8.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	350.0
	c)	PEG 400	200.0
	d)	Eudragit L	2.5
		TOTAL	602.5

9.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	312.5
	c)	Gelucir (e.g. Gelucir 42/12, 44/14 or 35/10	100.0
		TOTAL	462.5

10.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Saccharose monolaurate L-1695	312.5
	c)	Gelucir	100.0
	d)	Klucel LF	50.0
		TOTAL	512.5

The composition of example 1 is prepared by dissolving components (a) and (b) with stirring and warming over an oil bath at 100°C in component (c). The compositions of examples 2 to 10 are prepared analogously. In the case of examples 5 and 8 component (d) is dissolved in the initially obtained mixture of components (a) to (c). In the case of examples 6, 7 and 10 component (d) is suspended in (a) to (c).

The obtained compositions are filled, with warming, into hard gelatin capsules, size 1 (examples 1 to 4 and 9), or size 0 (examples 5 to 7 and 10), to give an encapsulated end-product with each capsule containing 50 mg cyclosporin (e.g. Ciclosporin) and suitable for administration for the prevention of transplant rejection or in the treatment of auto-immune diseases, e.g. on administration of from 1 to 5 capsules daily.

EXAMPLES

		INGREDIENT	RELATIVE AMOUNT (mg)
11.	a)	Cyclosporin (e.g. Ciclosporin)	100.0
	b)	Saccharose monolaurate L-1695	300.0
	c)	Plasdone XL	350.0
	d)	Avicel PH 102	150.0
	e)	Sodium-laurylsulfate	25.0
		TOTAL	925.0

12.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b¹)	Saccharose monolaurate L-1695	350.0
	b²)	Saccharose monostearate	50.0
	c)	Crospovidone	250.0
	d)	Elcema	150.0
	e)	Magnesium-stearate	30.0
		TOTAL	980.0

13.	a)	Cyclosporin (e.g. Ciclosporin)	50.0
	b)	Sacchorose monolaurate L-1695	160.0
	c)	Plasdone XL 10	200.0
	d¹)	Pharmacoate 603	25.0
	d²)	Avicel PH 101	75.0
	e)	Magnesium-stearate	20.0
		TOTAL	605.0

The above compositions 11 to 13 each suitably additionally comprise 25mg (f) tartaric acid and/or 50mg (g) dioctyl succinate, preferably both, giving an end weight: for composition 11 of 1,000mg; for composition 12 of 1,055mg; and for composition 13 of 6180mg.

Compositions 11 to 13 are prepared as follows: Components (a) and (b) are dissolved in absolute ethanol and the ethanol evaporated exhaustively at 50°C under reduced pressure. Components (c) to (e) are thoroughly admixed [with addition of (f) and (g) when used] employing conventional mixing techniques. The solid solution comprising [(a)+(b)] is milled to a fine powder and mixed uniformly into [(c)-(g)] and the resultant uniform mass pressed into tablets each containing 100, 50 or 25mg (a) and suitable for administration for the prevention of transplant rejection or in the treatment of auto-immune diseases, e.g. on administration of from 1 to 5 tablets daily.

EXAMPLES

	INGREDIENT	RELATIVE AMOUNT (mg)
14. a)	Cyclosporin (e.g. Ciclosporin)	50.0
b)	Saccharose monolaurate L-1695	312.5
c)	Paraffinum perliquidum	397.5
	TOTAL	760.0
15. a)	Cyclosporin (e.g. Ciclosporin)	50.0
b)	Saccharose monolaurate L-1695	312.5
c)	Silicon oil DC 200	397.5
	TOTAL	760.0

Components (a) and (b) are dissolved in absolute ethanol and the ethanol evaporated exhaustively at 50°C under reduced pressure. The obtained solid solution is milled to a fine powder and suspended uniformly in component (c). The obtained liquid suspension is filled into hard gelatin capsules, size 0 to give an encapsulated end-product with each capsule containing 50 mg cyclosporin (e.g. Ciclosporin) and suitable for administration for the prevention of transplant rejection or in the treatment of auto-immune diseases, e.g. on administration of from 1 to 5 capsules daily.

EXAMPLES

	INGREDIENT	RELATIVE AMOUNT (mg)
16. a)	Cyclosporin (e.g. Ciclosporin)	50.0
b)	Saccharose monolaurate L-1695	312.5
c)	Paraffinum subliquidum	372.5
d)	Paraffinum durum	25.0
	TOTAL	760.0
17. a)	Cyclosporin (e.g. Ciclosporin)	50.0
b)	Saccharose monolaurate L-1695	312.5
c)	Paraffinum perliquidum	397.5
d)	Aerosil	10.0
	TOTAL	770.0

Compositions 16 and 17 are prepared analogously to 14 and 15 above. In the case of composition 16, (c) and (d) are first combined by melting and intimately stirring together. The solid solution comprising [(a)+(b)] is then suspended in [(c)+(d)]. In the case of composition 17, (d) is suspended, together with [(a)+(b)] in (c).

Equivalent compositions to those of examples 1 to 17 above may be prepared by substitizing any other cyclosporin, e.g. [Nva]^2-Ciclosporin, for Ciclosporin as component (a), or substitizing any other fatty acid saccharide monoester, e.g. as hereinbefore set forth, for example raffinose monolaurate, for saccharose monolaurate as component (b) in each case in the same or equivalent amount or relative proportion.

Utility of compositions in accordance with the invention may be shovn in animal or clinical trials, for example performed as follovs:

BIOAVAILABILITY STUDY FOR COMPOSITIONS IN ACCORDANCE WITH THE INVENTION IN THE DOG

a) Test compositions

COMPOSITION I	as per example	1
COMPOSITION II	"	14

b) Test method

Groups of 8 beagle dogs (male, ca. 11-13kg) are used. Animals receive no food within 18 hours of administration of test composition but are alloved free access to vater until administration. Test compositions are administered by gavage, followed by 20ml NaCl 0.9% solution. The animals are alloved free access to food and vater three hours after administration of test composition.

2ml blood samples (or 5ml for the blank) are taken from the vena saphena and collected in 5ml plastic tubes containing EDTA at -15min. (blank), 30min., and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post administration. Blood samples are stored at -18°C pending assay.

Blood samples are analysed by RIA. Areas under the blood drug concentration versus time curves are calculated by the trapezoidal rule. Analysis of variance is performed with respect to AUC (area under curve), Cmax (maximum concentation) and Tmax (time of maximum).

c) Results

Calculated average AUC (in ng hr./ml^{-1}) and Cmax (in ng/ml^{-1}) values from typical trial runs are shown in the following table, together with calculated variation in response between test animals receiving the same composition (CV).

COMPOSITION	AUC (0-24h)	CV (%)	Cmax	CV%
I	3058	19.9	583	30.9
II	2894	14.91	544	19.7

As will be seen from the above table, compositions in accordance with the invention exhibit high bioavailability (AUC and Cmax.) coupled with relatively lov variability in subject response both for AUC and Cmax.

Comparable advantageous results may be obtained employing other compositions in accordance with examples 1 to 17 herein, in particular the compositions of example 1 to 10.

CLINICAL TRIAL

The advantageous properties of the compositions of the invention on oral administration may also be demonstrated in clinical trials, e.g. performed as follovs:

Trial subjects are adult volunteers, e.g. professionally educated males of from 30 to 55 years. Trial groups suitably comprise 12 subjects.

The following inclusion/exclusion criteria are applied:
Inclusion: Normal screening ECG; normal blood-pressure and heart rate; body

weight = 50-95kg.

Exclusion: Clinically significant intercurrent medical condition which might interfere with drug absorption, distribution, metabolism, excretion or safety; symptoms of a significant clinical illness in the two-week pre-trial period; clinically relevant abnormal laboratory values or electrocardiogram; need for concomitant medication during the entire course of the study; administration of any drug known to have a well-defined potential toxicity to a major organ system within the previous 3 months; administration of any investigational drug within 6 weeks prior to entry into the trial; history of drug or alcohol abuse; loss of 500ml or more blood within the past 3 month period; adverse drug reaction or hypersensitivity; history of allergy requiring drug therapy; Hep.-B/HIV-positive.

Complete physical examination and ECG is performed pre- and post-trial. The following parameters are evaluated within 1-month periods pre- and post-trial:
Blood: - red blood cell count, haemoglobin, hematocrit, erythrocyte sedimentation, white blood cell count, smear, platelet count and fasting glucose;
Serum/plasma - total protein and electrophoresis, cholesterol, triglycerides, Na^+, K^+, Fe^{++}, Ca^{++}, Cl^- creatinine, urea, uric acid, SGOT, SGPT, -GT, alkaline phosphatase, total bilirubin, α-amylase;
Urine - pH, microalbumin, glucose, erythrocytes, ketone bodies, sediment.
Creatinine clearance is also determined 1-month prior to trial entry.

Subjects each receive trial compositions in randomised sequence. Compositions are administered orally, once to a total dose of 150mg cyclosporin, e.g. Ciclosporin, and at least 14 days are alloved between each administration.

Administration is performed in the morning after an overnight fast of 10hrs. with only water alloved. Only caffein-free beverages are permitted within the 24hr. period following administration. Subjects are not alloved to smoke within the 12hr. period following administration. Subjects receive a standardised lunch 4 hrs. following administration.

Blood samples (2ml) are taken 1 hr. prior to administration and post-administration at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 14, 24, 28 and 32 hrs.. For determination of creatinine 2ml blood samples are taken immediately prior to administration and at 12, 24 and 48 hrs. post-administration. Samples for cyclosporin determination are collected in two EDTA coated polystyrene tubes (1ml each) at each time point and are deep frozen at -20°C after gentle agitation. Cyclosporin is assayed in whole blood using RIA with specific and/or non-specific MAB assay - detection limit in both cases = ca. 10ng/ml.

In trials carried out in accordance with the above protocoll, e.g. comparing the composition of example 1 in hard gelatin encapsulated form with the current Ciclosporin drink solution (Ciclosporin = 50mg, Labrafil = 150mg, ethanol = 50mg, maize oil = 213mg, in soft gelatin encapsulated form : content end weight = 463mg/dosage) as standard, substantially increased bioavailability levels for the example 1 composition are recorded in comparison with the standard as reflected in both AUC-(0-32 hrs) and Cmax values established. In addition, comparison of variation in whole blood Ciclosporin concentration (as determined by specific monoclonal RIA) with time following single administration of test compositions to a Ciclosporin dosage of 150mg, demonstrates marked reduction in variability of response between all subjects receiving composition in accordance with example 1 as compared with that for all subjects receiving the standard composition.

Similar or equivalent results may be obtained following oral administration of other compositions in accordance with the invention, e.g. as herein described in the examples.

CLAIMS

1. A pharmaceutical composition comprising
   a) a cyclosporin as active ingredient,
   b) a fatty acid saccharide monoester and
   c) a diluent or carrier,

   whereby

   i) component (c) is a solvent with respect to both components (a) and (b), components (a) and (b) each independently having a solubility in component (c) of at least 10% at ambient temperature; or

   ii) component (c) is a solvent with respect to both components (a) and (b), and components (a) and (c) are present in said composition in a ratio of 1:0.5 to 50 p.p.v. [(a):(c)]; or

   iii) component (c) is a solvent with respect to both components (a) and (b) and said composition is formulated in solid unit dosage form suitable for oral administration; or

   iv) component (c) comprises a poly-(C_{2-4}alkylene)-glycol having an average molecular weight of at most 7,000 or a viscosity at 50°C at ambient temperature of at most 15,000 mPa.s. or comprises a C_{3-5}alkylene polyol ether or ester; or

   v) said composition is, or is substantially, non-aqueous; or

   vi) component (c) comprises a solid polymeric carrier, an organosilicon oxide polymer or paraffinum per- or sub-liquidum and component (a) is present in said composition in solid solution in (b).

2. A pharmaceutical composition comprising
   a) a cyclosporin as active ingredient,
   b) a fatty acid saccharide monoester and
   c) a diluent selected from the group consisting of

c^1) ethanol
c^2) C_{2-4}alkylene glycols
c^3) C_{3-5}alkylene polyols
c^4) poly-(C_{2-4}alkylene)glycols
and mixtures thereof,

whereby

ii) components (a) and (c) are present in said composition in a ratio of 1:0.5 to 50 p.p.w. [(a):(c)]; or

iii) said composition is formulated in solid unit dosage form suitable for oral administration; or

iv) component (c) comprises a component (c^4) having an average molecular weight of at most 7,000 or a viscosity at 50° C of at most 15,000 mPa.s.; or

v) said composition is, or is substantially, non-aqueous.

3. A composition according to claim 2 wherein component (c) is selected from the group consisting of
c^2) 1,2-propylene glycol
c^3) glycerol and
c^4) polyethylene glycols having an average molecular weight of at most 7,000 or a viscosity at 50°C of at most 15,000 mPa.s..

4. A pharmaceutical composition comprising
a) a cyclosporin as active ingredient,
b) a fatty acid saccharide monoester and
c^2) 1,2-propylene glycol,

whereby

ii) components (a) and (c^2) are present in said composition in a ratio of 1:0.5 to 50 p.p.w. [(a):(c^2)]; or

iii) said composition is formulated in solid unit dosage form suitable for oral administration; or

v) said composition is, or is substantially, non-aqueous.

5. A pharmaceutical composition comprising
a) a cyclosporin as active ingredient,
b) a fatty acid saccharide monoester and
c^5) a C_{3-5}alkylene polyol ether or ester.

6. A composition according to claim 5, wherein component (c^5) comprises a transesterification product of a natural or hydrogenated vegetable oil and a polyethylene glycol.

7. A composition according to claim 6, wherein component (c^5) comprises a transesterification product of a natural or hydrogenated vegetable oil and a polyethylene glycol having a molecular weight of from 500 to 4,000.

8. A composition according to claim 6 or 7, wherein component (c^5) comprises a transesterification product of a natural or hydrogenated vegetable oil, a polyethylene glycol and glycerol.

9. A composition according to any one of claims 5 to 8, wherein components (a) and (c^5) are present in a ratio of 1:0.5 to 50 p.p.w.

10. A composition according to any one of claims 1 to 9, wherein components (a) and (c) or, in the case of claim 4, (c^2), or in the case of claims 5 to 9, (c^5), are present in a ratio of 1:1 to 10 p.p.w. [(a):(c)/(c^2)/(c^5)].

11. A composition according to claim 10, wherein the ratio is 1:1.5 to 2.5 p.p.w.

12. A composition according to any one of claims 1 to 11, wherein components (a) and (b) are present in a ratio of 1:3 to 200 p.p.w. [(a):(b)].

13. A composition according to claim 12, wherein the ratio is 1:5 to 20 p.p.w.

14. A composition according to claim 13, wherein the ratio is 1:6 to 6.5 p.p.w.

15. A pharmaceutical composition comprising
a) a cyclosporin as active ingredient in solid solution in
b) a fatty acid saccharide monoester, and
c^6) a solid polymeric carrier.

16. A composition according to claim 15, wherein component (c^6) comprises a polyvinylpyrrolidone.

17. A composition according to claim 15 or 16, wherein components (a) and (b) are present in a ratio of 1:2 to 20 p.p.w. [(a):(b)].

18. A composition according to claim 17, wherein the ratio is 1:3 to 8 p.p.w.

19. A composition according to any one of claims 15 to 18, wherein component (c^6) is present in an amount of at least 10% by weight based on the total weight of the composition.

20. A composition according to claim 19, wherein component (c^6) is present in an amount of from 15 to 50% by weight based on the total weight of the composition.

21. A composition according to any one of claims 15 to 20, additionally comprising (d) a water swellable component.

22. A composition according to claim 21, wherein components (d) and (c^6) are present in a ratio of 1:0.5 to 4 p.p.w. [(d):(c^6)].

23. A composition according to any one of claims 1 to 23 in unit dosage form and comprising from 2 to 200mg component (a) per unit dosage.

24. A composition according to claim 23 comprising from about 10 or 20 to about 100mg component (a) per unit dosage.

25. A pharmaceutical composition comprising
a) a cyclosporin as active ingredient,
b) a fatty acid saccharide monoester and
c²) 1,2-propyleneglycol
said composition being in unit dosage form and comprising from about 20 to about 100mg of component (a) per unit dosage, components (a) and (b) being present in said composition in a ratio of 1:3 to 200 p.p.w. [(a):(b)] and components (a) and (c) being present in said composition in a ratio of 1:0.5 to 50 p.p.w.

26. A composition according to claim 25, wherein components (a) and (b) are present in a ratio of 1:5 to 10 p.p.w. and components (a) and (c) are present in a ratio of 1:1.5 to 2.5 p.p.w.

27. A composition according to any one of claims 1 to 26 in soft or hard gelatin encapsulated, oral dosage form.

28. A composition according to any one of claims 1 to 27 additionally comprising a stabilizor or buffering agent.

29. A composition according to claim 28 buffered to a pH of from 3 to 8.

30. A composition according to any one of claims 1 to 29, wherein component (a) is Ciclosporin or [Nva]²-Ciclosporin.

31. A composition according to any one of claims 1 to 30, wherein component (b) comprises a water soluble fatty acid saccharide monoester.

32. A composition according to claim 31, wherein component (b) comprises a C_{6-18} fatty acid di- or tri-saccharide monoester.

33. A composition according to claim 32 wherein component (b) comprises raffinose or saccharose monolaurate.

34. A composition as claimed in any one of the preceding claims, substantially as hereinbefore described with reference to anyone of the accompanying examples.

Published 1990 at The Patent Office, State House, 66 71 High Holborn, London WC1R 4TP. Further copies may be obtained from The Patent Office Sales Branch, St Mary Cray, Orpington, Kent BR5 3RD. Printed by Multiplex techniques ltd. St Mary Cray, Kent, Con 1/87